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Tang, Ivan ; Turnbull, Chris D ; Sen, Dushendree ; Craig, Sonya ; Kohler, Malcolm ; Stradling, John R

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Effect of CPAP on cardiovascular events in minimally symptomatic OSA: long-term follow-up of the MOSAIC randomised controlled trial

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ABSTRACT

The effect of continuous positive airway pressure (CPAP) on cardiovascular events is uncertain in minimally symptomatic obstructive sleep apnoea. Previous 2-year follow-up data from the Multicentre Obstructive Sleep Apnoea Intervention Cardiovascular (MOSAIC) trial showed a marginal reduction in cardiovascular events with CPAP therapy. We now present long-term MOSAIC study follow-up data. Median (first quartile, third quartile) follow-up was 5.0 (2.2, 5.0) and 3.7 (1.5, 5.0) years for CPAP and standard care, respectively. Compared to standard care, CPAP had no statistically significant effect on the risk of cardiovascular events (HR=0.83, p=0.54, 95% CI 0.46–1.51).

INTRODUCTION

The Multicentre Obstructive Sleep Apnoea Intervention Cardiovascular (MOSAIC) trial was a multicentre, randomised controlled trial investigating the effect of continuous positive airway pressure (CPAP) treatment on calculated cardiovascular risk and daytime sleepiness in patients with minimally symptomatic obstructive sleep apnoea (OSA). Although CPAP improved daytime sleepiness, it did not improve calculated cardiovascular risk at 6 months.[1]

Two-year follow-up data of the Oxford patients found a statistically significant but marginal reduction (absolute reduction 9.6%, 95% CI 0% to 19%, p=0.05) in new cardiovascular events in the CPAP group compared with standard care.[2] This contrasts with the Sleep Apnoea Cardiovascular events (SAVE) Study which showed no improvement in new cardiovascular events following CPAP therapy.[3]

Despite evidence from observational studies, improvement in cardiovascular events resulting from CPAP in OSA remains unendorsed by randomised controlled trials.[4]

METHODS

We report long-term follow-up from all patients from a single centre of the MOSAIC trial. The MOSAIC trial was a multicentre, randomised controlled parallel, hospital trial in patients with confirmed OSA (oxygen desaturation index >7.5/hour) but insufficient symptoms to mandate CPAP therapy.[1]

Patients were randomised to standard care or auto-adjusting CPAP therapy. The Oxford cohort was followed-up for a maximum of 5 years, and data were collected on new cardiovascular events. Data were analysed on an intention-to-treat basis. We prospectively recorded the occurrence of new cardiovascular events, including those leading to death. Cardiovascular events included angina, myocardial infarction, hypertension, peripheral vascular disease, atrial fibrillation, cardiac failure, stroke, transient ischaemic attack, coronary intervention and coronary artery bypass graft. Event-free survival was analysed using the log-rank test and Cox proportional HRs with multivariate analyses adjusted for age, baseline cardiovascular risk score and body mass index (BMI). A per protocol analysis was carried out of those patients who were randomised to CPAP who had usage of >4 hour/night at last follow-up.

At 2-year follow-up 9% and 4% in the standard care and CPAP arm groups experienced new events per year of follow-up.[2] In order not to miss similar difference event rate over 5 years, with 80% power and two-sided alpha of 0.05, 120 patients were needed.

RESULTS

All 191 patients from a single centre are included in this follow-up analysis, with 94 initially randomised to the CPAP arm and 97 to the standard care arm. Patient characteristics are displayed in table 1. Forty-three

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Table 1 Patient characteristics by treatment group. Data are displayed as mean±standard deviation, median (first quartile, third quartile) or number (%)

	CPAP	Standard care	CPAP where usage >4 hour/night
Number	94	97	25
Baseline age (years)	58.2±7.1	57.7±7.6	57.2±6.3
Male	81 (86%)	84 (87%)	23 (92%)
Female	13 (14%)	13 (13%)	2 (8%)
Baseline BMI (kg/m^2)	32.6±5.7	32.4±5.3	32.5±4.0
ODI at presentation	10.7 (4.7, 17.9)	10.1 (5.9, 18.2)	11.5 (3.6, 30.4)
Baseline hypertension	45 (48%)	47 (49%)	10 (40%)
Baseline diabetes mellitus	15 (16%)	24 (25%)	3 (12%)
Baseline atrial fibrillation	4 (4%)	4 (4%)	1 (4%)
Baseline ischaemic heart disease	11 (12%)	18 (19%)	2 (8%)
Baseline cerebrovascular disease	6 (6%)	2 (2%)	2 (8%)
Current smoker	10 (11%)	17 (18%)	24 (17%)
Length of follow-up (years)	5.0 (2.2, 5.0)	3.7 (1.5, 5.0)	5.0 (5.0, 5.0)
Number of crossovers	43 (46%)	16 (17%)	0 (0%)
Numbers using CPAP at final follow-up	38 (40%)	10 (10%)	25 (100%)
Adherence in those using CPAP at final follow-up (hours:min/night)	5:51 (3:22, 6:58)	3:32 (1:00, 6:56)	6:44 (5:51, 7:10)

BMI, body mass index; CPAP, continuous positive airway pressure; ODI, Oxygen desaturation index >4%.

patients (46%) randomised to CPAP crossed over and stopped CPAP. Those randomised to CPAP and still using CPAP had good mean adherence, with median of mean usage of 5:51 hours:min/night (Interquartile range 3:22–6:58) at the end of the follow-up period; and 10 standard care subjects (10%) had were using CPAP with median of mean usage of 3:32 hours:min/night (Interquartile range 1:00–6:55) by the end of the period.

There were 25 cardiovascular events in the CPAP group, compared with 32 in the standard care group. There was no significant difference in the univariate risk of cardiovascular events between CPAP and standard care (HR=0.83, p=0.54, 95% CI 0.46 to 1.51, figure 1). Multivariate adjustments for age, BMI and baseline cardiovascular risk score did not alter these results (HR=0.82, p=0.52, 95% CI 0.45 to 1.50). A per protocol analysis of the risk of cardiovascular events in patients with CPAP usage >4 hour/night was also not significant, compared with standard care (HR=1.3, p=0.46, 95% CI 0.61 to 2.94).

DISCUSSION

We have not shown CPAP to significantly impact cardiovascular event rates in minimally symptomatic OSA. This contrasts with our previous publication showing a reduction in cardiovascular events after 2 years of follow-up,[2] hence the importance of reporting these longer term data. These results are in keeping with the much larger SAVE Study,[3] which found that CPAP did not reduce cardiovascular events in patients screened for OSA following presentation to cardiovascular clinics.

Long-term follow-up in this study was limited by the small trial population, and thus wide confidence intervals of the estimates. However, given the marginal reduction in cardiovascular events observed at the 2 year follow-up, these data are important to report. The median length of follow-up was also longer in the CPAP arm as these patients were motivated to stay in touch to maintain their equipment. However, survival analyses take length of follow-up into account.

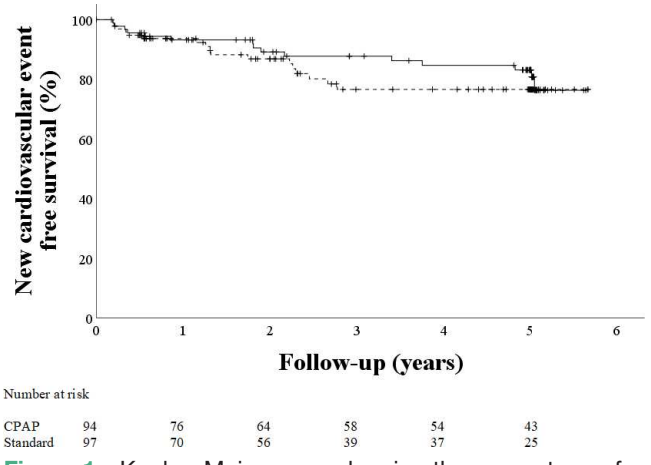

Figure 1 Kaplan-Meier curve showing the percentage of patients without the occurrence of a cardiovascular event by the number of follow-up days for standard care (dotted line) or CPAP solid line. Log rank p=0.54. Cox proportional HR=0.83 (p=0.54, 95% CI 0.46 to 1.51). CPAP, continuous positive airway pressure.

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A theme consistent between MOSAIC, SAVE and the more recent Assessment of the Effect of CPAP on Energy and Vitality in Mild OSA (MERGE) trial, was the improvement of quality of life and symptoms with CPAP in even mild OSA.[1–3 5] It is notable that the average usage of CPAP at the end of long-term follow-up, among those who did continue treatment was good (>5 hour/night). This demonstrates that there are patients who adhere to CPAP in the long-term despite minimal symptoms. However, even among these individuals with good long-term adherence to CPAP there was no suggestion of a reduction in cardiovascular events.

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Contributors SC, MK and JRS conceived the initial trial and were responsible for trial design. IT and DS were responsible for data collection. IT and CDT were responsible for data analysis, literature searches and preparing the first draft of the manuscript. All authors viewed, commented and took responsibility for the final manuscript.

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Data availability statement Data are available upon reasonable request including appropriate ethical approval. Qualified researchers may request access to patient level data and related study documents including the study protocol. Requests will be reviewed for scientific merit. Patient level data will be deidentified and study documents will be redacted to protect the privacy of trial participants. Please contact the corresponding author.

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